

## Prevalence of hypothyroidism in a cohort of Saudi women with heart failure and effect on systolic and diastolic function

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### Abstract

**Objectives:** To determine the prevalence of hypothyroidism in a cohort of Saudi women with heart failure; to define the demographic variables associated with heart failure; and the impact of hypothyroidism on systolic function in relation to non-hypothyroidism group.

**Methods:** The cross-sectional cohort study was conducted at King Abdulaziz University Hospital, Jeddah, Saudi Arabia, and comprised all women diagnosed with heart failure who were seen in the Cardiology outpatients clinic between February 2010 and March 2013. All of them were subjected to complete medical history and clinical examination, including complete cardiac clinical examination, electrocardiogram, echocardiography, blood pressure reading as well as thyroid examination. Laboratory tests were performed for thyroid stimulating hormone, total cholesterol, triglycerides, low-density lipoprotein and high-density lipoprotein.

**Results:** Of the 111 patients, 37 (33.3%) had hypothyroidism ( $p < 0.001$ ), and 16 (14.4%) of them showed subclinical hypothyroidism. The mean value for thyroid stimulating hormone was  $4.79 \pm 4.98$  U/L. There was a significant negative correlation between thyroid stimulating hormone and ejection fraction.

**Conclusion:** There was close relation between hypothyroidism and heart failure. Further large-scale studies are recommended for early detection of hypothyroidism.

**Keywords:** Congestive heart failure, Diastolic function, Ejection fraction, Hypothyroidism, Systolic function, Thyroid stimulating hormone, Women. (JPMA 65: 1300; 2015)

### Introduction

Heart failure (HF) is a common outcome of different forms of heart diseases.<sup>1</sup> The American College of Cardiology (ACC) defines HF as a complex clinical syndrome that impairs the ability of the ventricle to fill with or eject blood. HF can be an outcome of a defect in the myocardial contractility (Myocardial failure) or by diastolic HF which is defined as impairment of the filling of the left ventricle (LV) with preserved contractility, or the combination of both systolic and diastolic dysfunctions.<sup>2,3</sup> HF is responsible for a high rate of hospitalisation and it is a major cause of morbidity and mortality in Europe and in the United States.<sup>4,5</sup> Despite progress in treating HF in the last 15 years, the prognosis of this dysfunction remains poor.<sup>6</sup> The treatment of HF has made dramatic progress over the last 15 years, but its prognosis is still poor.<sup>6</sup> Recently, untreated overt hyperthyroidism and hypothyroidism have been recognised as common causes for HF.<sup>7-10</sup> Moreover, persistent subclinical thyroid dysfunction is increasingly being recognised to be associated with the development of HF in patients with and without underlying cardiac disease.<sup>11-13</sup> Thyroid dysfunction is a modifiable and manageable risk factor in

HF patients or patients who are at risk of HF.<sup>7,9</sup> The cardiac manifestations of subclinical hypothyroidism are mainly in the form of systolic dysfunction.<sup>14</sup> Adverse cardiovascular effects of hypothyroidism has been identified in several previous studies.<sup>7,9</sup> Most of the studies focused on systolic/diastolic dysfunction in hypothyroidism. Early identification of patients with subclinical hypothyroidism may lead to early treatment and thereby favourable effect on cardiovascular morbidity and mortality.<sup>15</sup> Thyroid disorders commonly affect females and a smaller percentage of adult males.<sup>16</sup> The commonest two thyroid disorders are Graves' and Hashimoto's disease. They affect females more commonly than males and as many as 9% to 15% of the adult female population is affected.<sup>16</sup> This gender-specific prevalence is almost certainly an outcome of the underlying autoimmune mechanism causing both the diseases.<sup>17</sup>

The current study was conducted to find out the prevalence of hypothyroidism in a cohort of Saudi women with HF. It also aimed at defining its related variables and the impact of hypothyroidism on systolic and diastolic cardiac functions.

### Patients and Methods

The cross sectional cohort study was conducted at King Abdulaziz University Hospital (KAUH), the largest tertiary

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care centre in Jeddah, Saudi Arabia, and comprised all women diagnosed with HF and seen at the Cardiology outpatients clinic from February 2010 to March 2013.

Those included were women who had stable HF at the time of inclusion defined as stable clinical condition which meant they had clear lung fields on examination, stable electrocardiogram (ECG with no new changes), and who were on conventional anti-failure medical therapy for at least 3 months. Patients who had unstable or fluctuating HF and those who had incomplete data were excluded.

For each patient, complete sheet of medical history was obtained with stress on the duration of the cardiac disease, onset of the disease, medications, smoking habit, hereditary factors with first-degree relatives and history of thyroid dysfunction and medications. Surgical history for thyroidectomy, history of diabetes mellitus (DM) and hypertension were also determined. Conventional cardiac examination with auscultation, ECG, and systolic and diastolic blood pressure measurements were performed for each patient. Complete examination of the thyroid gland. Blood samples were taken from all the patients for thyroid function, haemoglobin concentration and lipid profile via measuring the levels of thyrotropin or thyroid stimulating hormone (TSH), tri-iodothyronine (T3), thyroxin (T4), total cholesterol (TCL), triglycerides (TG), low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol. Echocardiography was done for all studied patients to determine end systolic dimension (ESD), end diastolic dimension (EDD), and ejection fraction (EF%).

Severe hypothyroidism was defined as TSH level higher than 15 and low T4 and T3 in the presence of symptoms of hypothyroidism. Hypothyroidism was defined as TSH 9–14.9 with low T4 and T3 in the presence of symptoms of hypothyroidism. Isolated TSH elevation with normal T3, and T3 in the absence of hypothyroidism symptoms was defined as subclinical hypothyroidism.

**Table-3:** Comparison of the Lipids profiles.

Lipid profile	Elevated value		Normal		P value*
	Number of patient	Mean SD	Number of patients	Mean SD	
Total cholesterol	20 (18%)	6.2±0.62	91 (82%)	3.8±0.92	0.022
Triglycerides	17 (15.3%)	1.4±0.6	94 (84.7%)	1.5±1	0.033
LDL	24 (21.6%)	4.1±0.44	87 (78.4%)	2.3±0.1	< 0.001
HDL	27 (24.3%)	2.22±0.63	66 (59.5%)	0.99±0.3	< 0.001

\*Test of significance was performed between elevated and normal values.

LDL: Low-density lipoprotein.

HDL: High-density lipoprotein.

Descriptive data was noted and continuous variables were expressed as mean ± standard deviation (SD). One-way Chi square was used to study the effect of association of different variables with HF. Student's t test was used to study the difference of serum lipids levels between patients with normal levels and patients with high levels. One-way analysis of variance (ANOVA) was used to study the difference in the mean serum TSH between the three categories of hypothyroidism. Microsoft Excel statistical software (2010) was used and level of statistical significance was set at  $p < 0.05$ .

## Results

There were a total of 111 patients with a mean age of  $59.1 \pm 15.7$  years (range: 20–88 years). Clinical characteristics of the patients were within the normal range except weight, the mean of which was  $83.7 \pm 11.9$  kg (range: 58–112 kg). Mean body mass index (BMI) was  $30.5 \pm 6.5$  kg/m<sup>2</sup>. DM, hypertension and smoking were frequently observed as highly significant risk factors ( $p < 0.001$  each), while dyslipidaemia showed less

**Table-1:** Prevalence of risk factors.

Risk factor	Present		Absent		P value
	No.	%	No.	%	
Diabetes mellitus	94	84.7	17	15.3	<0.001*
Hypertension	92	82.9	19	17.1	<0.001
Dyslipidaemia	41	36.9	70	63.1	0.01
Smoking	5	4.5	106	95.5	<0.001

\*Prevalence of diabetes and hypertension were significantly elevated in this study population ( $P < 0.001$ ).

**Table-2:** Prevalence of hypothyroidism.

Hypothyroidism	Number of patients	%
Severe hypothyroidism	6	5.4
Hypothyroidism	15	13.5
Subclinical hypothyroidism	16	14.4
Total	37	33.3

**Table-4:** Mean echocardiographic findings.

	Mean ± SD	Range	Referral values
ESD	4.23 ± 0.83	2.5 - 6.8	Up to 3.5 cm
EDD	5.47 ± 0.67	3.0 - 7.6	Up to 4.5 cm
EF%	31.6 ± 8.53	15 - 60	More than 35%

Values showing abnormal mean echocardiographic parameters in studied cohort.

SD: standard deviation

ESD: End systolic dimension

EDD: End diastolic dimension

EF: Ejection fraction.

significant value ( $p=0.01$ ) (Table-1).

Hypothyroidism was found in 37(33.3%) patients ( $p<0.001$ ). Majority of patients who had hypothyroidism had subclinical hypothyroidism (Table-2),

Mean urea level was 108.4±84.3 mg/dl; creatinine 1.5±1.2 mg/dl (range: 0.6-6.2); haemoglobin 12±7.4 g/dl; TC 162±50 mg/dl; TG 150.4±88.4 mg/dl; LDL 104.2±38.6 mg/dl; TSH 4.8±5 Pmol/L; T3 3.7±1.4pmol/l;T4 13.7±1 Pmol/l.

Besides, 76(68.4%) patients had elevated urea and 42(38%) patients had creatinine above the upper reference range. The mean TSH level was significantly different between the three categories of hypothyroidism ( $p>0.001$ ). Serum lipids showed significant difference between patients with high levels compared with those with normal levels for cholesterol, TG, LDL and HDL (Table 3).

Echocardiography findings were evaluated for each patient (Table-4) and the mean echocardiography parameters showed abnormal findings. Using simple regression model, there was significant negative correlation between EF and the TSH level ( $r = - 0.7489$ ;  $R^2 = 0.5608$ ).

Only 4(3.6%) patients had atrial fibrillation (AF).

## Discussion

Hypothyroidism is recognised to cause many effects on the cardiovascular system, such as impaired cardiac contractility, decreased cardiac output, increased systemic vascular resistance, and cardiac atrophy.<sup>18-20</sup> This study on Saudi women with HF shows the prevalence of hypothyroidism in this cohort. One-third patients had hypothyroidism of different severity. The second observation in this cohort, the higher the TSH level the lower the EF, stresses on the effect of hypothyroidism on the cardiac function.

Multiple clinical and experimental studies had demonstrated the relationship between thyroid hormone and the cardiovascular system.<sup>21-32</sup> This relationship has

been recently confirmed by remarkable changes in cardiac structure and function in patients with persistent subclinical thyroid dysfunction.<sup>11-13,18,23</sup> Hypothyroidism can increase the risk of HF events<sup>11,12</sup> and cause decrease in heart rate and stroke volume that will ultimately result in reduced cardiac output.<sup>25</sup> Systolic and diastolic functions are both hindered at rest and during exercise, thus impairing patients' quality of life.<sup>27</sup> Impaired diastolic functions will cause reduction in the cardiac preload and reduced blood volume.<sup>28</sup> Deranged vascular function is another complication that might develop in cases of overt and mild thyroid hormone deficiency.<sup>28-32</sup> An increased cardiovascular risk in the form of coronary artery disease (CAD) or HF has been reported in patients with various degrees of hypothyroidism.<sup>11</sup>

In this study, the mean TSH value exceeded the normal referral values which indicate the tendency for hypothyroidism in HF patients. The majority of patients in this cohort were overweight with mean weight of 83.7±11.9kg. Obesity and overweight has been considered a predisposing risk factor for DM, hypertension and HF in many studies.<sup>33-35</sup> DM represents the highest risk factor that was associated with HF in this cohort as it is found in 84.7% of the patients. Similarly, hypertension was a frequently reported risk factor in about 83% patients. Dyslipidaemia and smoking were less frequently reported as risk factors for cardiac disease among this cohort. Dyslipidaemia was associated with poor outcome in patients with CHF.<sup>33</sup> Lipid profile showed normal values for both cholesterol and TG. This may be explained by individual variation of lipid profiles in patients with HF. One study<sup>36</sup> found that the mean serum cholesterol was significantly raised in both subclinical and overt hypothyroidism with respect to control group. The association of hypothyroidism with elevated serum lipid levels had been previously recognised. Overt hypothyroidism is characterised by hypercholesterolaemia and a marked increase in LDL and Apolipoprotein B.<sup>37</sup> The prevalence of overt hypothyroidism in patients with hypercholesterolemia is estimated to be 1.3% to 2.8%, and 90% patients with hypothyroidism had hypercholesterolaemia.<sup>37-39</sup> Lipid profile changes are also evident in subclinical hypothyroidism. Specifically, some studies have demonstrated that LDL is increased in subclinical hypothyroidism and is reversible with thyroid hormone replacement,<sup>40</sup> whereas other studies have shown increased total cholesterol in subclinical hypothyroidism with no changes in LDL. The reported mechanisms for the development of hypercholesterolaemia in hypothyroidism include decreased fractional clearance of LDL by a reduced number of LDL receptors in the liver in

addition to decreased receptor activity.<sup>41</sup> The catabolism of cholesterol into bile is mediated by the enzyme cholesterol 7 $\alpha$ -hydroxylase.<sup>42</sup> This liver-specific enzyme is negatively regulated by T3 and may contribute to the decreased catabolism and increased levels of serum cholesterol associated with hypothyroidism.<sup>41</sup> The increase of serum lipid levels in subclinical hypothyroidism as well as in overt disease are potentially associated with increased cardiovascular risk.<sup>43</sup> Treatment with thyroid hormone replacement to restore euthyroid status reverses the risk ratio.<sup>41</sup> If untreated, the dyslipidaemia together with the diastolic hypertension associated with hypothyroidism may further predispose the patient to atherosclerosis.<sup>44,45</sup>

## Conclusion

The study showed clear association of hypothyroidism with HF among Saudi females with cardiac disease. In addition, hypothyroidism seemed to play a role in the deterioration of cardiac function in females with HF. The findings stress the importance of early detection and effective treatment of cardiac abnormalities in patients affected by thyroid disorders. Close cooperation between endocrinologists and cardiologists is essential to optimise the treatment of such patients and to improve the prognosis of severe cardiac involvement in patients with severe, mild and subclinical thyroid dysfunction. Controlling hypothyroidism in HF patients is recommended as it affects prognosis adversely.

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